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Association of the Recovery of Objective Abnormal Cerebral Perfusion With Neurocognitive Improvement After Carotid Revascularization

Ching-Chang Huang, MD,* Ying-Hsien Chen, MD,* Mao-Shin Lin, MD,*† Cheng-Hsin Lin, MD,†‡ Hung-Yuan Li, MD, PhD,* Ming-Jang Chiu, MD, PhD,§‖ Chi-Chao Chao, MD,§ Yen-Wen Wu, MD, PhD,*¶#** Ya-Fang Chen, MD,†† Jen-Kuang Lee, MD,‡‡ Ming-Jiuh Wang, MD, PhD,§§ Ming-Fong Chen, MD, PhD,* Hsien-Li Kao, MD*

Taipei and New Taipei City, Taiwan

Objectives This study sought to report the effect of carotid artery stenting (CS) on neurocognitive function (NCF) in patients with severe carotid artery occlusive disease, depending on baseline brain perfusion status.

Background The effect of CS on NCF has been controversial.

Methods We prospectively enrolled 61 patients with carotid artery disease (22 with occlusion, 39 with severe stenosis) in whom CS was attempted. Computed tomography perfusion and NCF assessments including Mini-Mental State Examination (MMSE), Alzheimer Disease Assessment Scale–Cognitive subscale (ADAS-Cog), verbal fluency, and Color Trails Test Parts 1 and 2 were applied before and 3 months after intervention.

Results Successful recanalization was achieved in 14 of 22 occlusion patients (64%) and in all 39 severe stenosis patients. Two cases were excluded due to procedural cerebral complications. The patients were divided into 3 groups: group 1 ($n = 8$) consisted of patients with abnormal baseline ipsilateral cerebral perfusion in whom CS failed; group 2 ($n = 33$) consisted of patients with abnormal baseline ipsilateral cerebral perfusion in whom CS was successful; and group 3 ($n = 19$) consisted of patients without abnormal baseline ipsilateral cerebral perfusion in whom CS was successful. The demographics and baseline NCF were similar among groups. Only in group 2 was there significant improvement in ADAS-Cog (pre-procedure median [interquartile range]: 6 [4 to 9] vs. post-procedure: 5 [3 to 7], $p = 0.002$), MMSE (pre-procedure: 27 [25 to 28] vs. post-procedure: 28 [25 to 29], $p = 0.004$) and Color Trails Test Part 1 (pre-procedure: 100 [78.5 to 136.5] s vs. post-procedure: 97 [60 to 128.5] s, $p = 0.003$) after CS. Significant difference in changes from baseline was observed only in the Color Trails Test Part 1 among groups (group 1 vs. 2 vs. 3: 1.5 [−14 to 11.5] vs. −12.5 [−36.5 to 0.5] vs. −0.5 [−11 to 27], $p = 0.0159$). Significant correlation between the change of ipsilateral brain perfusion and MMSE ($r = -0.33$, $p = 0.01$) was also identified.

Conclusions Successful CS for severe carotid stenosis/occlusion improves NCF, but only in patients with objective baseline abnormal cerebral perfusion. (J Am Coll Cardiol 2013;61:2503–9) © 2013 by the American College of Cardiology Foundation

Reducing embolic stroke by carotid artery stenting (CS) and carotid endarterectomy (CE) in patients with severe internal carotid occlusive disease has been well proven (1,2). In addition, neurocognitive function (NCF) is being increasingly recognized as an important outcome measure. Cognitive impairment and decline were found in patients with asymptomatic high-grade stenosis of the left internal carotid artery (ICA) (3), and hypoperfusion may be a potential cause (4). It is intuitive that reopening a stenotic vessel and restoring blood flow to the brain would certainly

From the *Department of Internal Medicine, National Taiwan University Hospital, Taipei, Taiwan; †Graduate Institute of Clinical Medicine, Medical College, National Taiwan University, Taipei, Taiwan; ‡Department of Surgery, National Taiwan University Hospital, Taipei, Taiwan; §Department of Neurology, National Taiwan University Hospital, Taipei, Taiwan; ‖Department of Psychology, National Taiwan University, Taipei, Taiwan; ¶Department of Nuclear Medicine, National Taiwan University Hospital, Taipei, Taiwan; #Department of Nuclear Medicine and Cardiovascular Medical Center (Cardiology Division), Far Eastern Memorial Hospital, New Taipei City, Taiwan; **National Yang-Ming University School of Medicine, Taipei, Taiwan; ††Department of Medical Imaging, National Taiwan University Hospital, Taipei, Taiwan; ‡‡Department of Laboratory Medicine, Far Eastern Memorial Hospital, New Taipei City, Taiwan; and the §§Department of Anesthesiology, National Taiwan University Hospital, Taipei, Taiwan. The authors have reported that they have no relationships relevant to the contents of this paper to disclose. The first 3 authors contributed equally to this work and should be considered joint first authors.

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Abbreviations and Acronyms

ADAS-Cog = Alzheimer Disease Assessment Scale–Cognitive subscale
CBF = cerebral blood flow
CBV = cerebral blood volume
CE = carotid endarterectomy
CS = carotid artery stenting
CT = computed tomography
CTP = computed tomography perfusion
ICA = internal carotid artery
ICAO = internal carotid artery occlusion
MMSE = Mini-Mental State Examination
NCF = neurocognitive function
NIHSS = National Institutes of Health Stroke Scale

have favorable neurocognitive effects, but previous studies have provided inconsistent results (5–8). Several factors may contribute to the inconsistency, including the diversity of the patient population, the difference in baseline cerebral perfusion status, variability of surgical and endovascular techniques, the differences in neuropsychological testing methodology, and the possible learning effect on repeated tests. Procedural emboli, temporary flow interruption, and general anesthesia may also offset the benefit of improved cerebral hemodynamics.

Our previous work has demonstrated that successful CS can improve global cognitive functions as well as attention and psychomotor processing speed in patients with chronic internal carotid artery occlusion (ICAO) (9), even in asymptomatic patients (10). The results implied the reversibility of cognitive function in an ischemic hemisphere after restoring cerebral perfusion. Therefore, we conducted the present study with an expanded patient cohort to assess the neurocognitive change after CS in all patients with severe ICA disease, analyzed according to baseline perfusion status of the ipsilateral hemisphere and procedural result.

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Methods

Patients. All patients were 18 years of age or older. From July 2008 to January 2010, endovascular intervention was attempted in 61 consecutive patients with severe ICA stenosis or ICAO. The indication was diameter stenosis >60% in symptomatic patients, and >80% in asymptomatic (2). Patients with documented ICAO would be followed up clinically for at least 2 months, and CS was only attempted in patients with ischemic symptom progression or objective hemisphere ischemia (11,12). We excluded patients with ischemic stroke within 2 weeks, vascular disease precluding catheter-based techniques, intracranial aneurysm or arteriovenous malformation, history of bleeding disorder, any surgery planned within 30 days, life expectancy <1 year, educational level below elementary school, aphasia, right-sided hemiparesis, marked depression, or at least moderate dementia. Brain computed tomography (CT) perfusion (CTP) with Diamox (acetazolamide) stress and a battery of neuropsychological tests were performed before and 3 months after carotid intervention.

NCF evaluation. Cognitive function evaluation was performed by an independent clinical psychologist, who was blinded to the outcomes of the intervention. Cognitive assessment of global measures included the Mini-Mental State Examination (MMSE) (13,14) and Alzheimer Disease Assessment Scale–Cognitive subscale (ADAS-Cog), a widely used rating instrument assessing memory, orientation, language, and ideational and constructional praxis. ADAS-Cog scores range from 0 to 70, with a higher score indicating lower performance (15,16). Additional tests covering neuropsychological functions, such as executive function, working memory, and attention, are compatible with the concept of VADAS-Cog and are suitable for our patients with vascular-related cognitive impairment (17,18). Relevant tasks included verbal fluency (category naming: fruits, vegetables, and fishes) and Color Trails Test Parts 1 and 2 (17,19). The Color Trails Test was used to replace the more educational-dependent conventional Trail Making Test.

Interventional procedure and clinical follow-up. Aspirin 100 mg and clopidogrel 75 mg/day were started 7 days before the procedure. CS procedure was done with techniques described in the literature (2,20). The definition of ICAO and the details of the interventional technique were also described previously (11,12). Technical success was defined as implantation of stents after recanalization of the lesion, with final residual diameter stenosis ≤20% and Thrombolysis In Myocardial Infarction flow grade 3 antegrade. All patients were sent to the intensive care unit for overnight hemodynamic and neurological monitoring, where systolic blood pressure was carefully maintained within 100 to 140 mm Hg. Aspirin and clopidogrel were continued for ≥3 months after successful intervention. Complete neurological examinations, including assessment of National Institutes of Health Stroke Scale (NIHSS) and Barthel Index, were done by an independent neurologist before, 1 week, and 3 months after the procedure. Neurological sequelae, intracranial hemorrhage, and death were recorded. Follow-up ultrasound examination was scheduled at 3 months after the intervention.

CT follow-up and analysis. CTP and CT angiography by a multidetector CT scanner was scheduled before and 3 months after the procedure. Assessment of cerebral perfusion (before and after the procedure) was performed by 2 independent investigators who were blinded to clinical and angiographic outcomes. CT perfusion data were analyzed separately off-line at a workstation using commercial software (CT Perfusion 3, Advantage 4.2, GE Healthcare, Little Chalfont, United Kingdom). Cerebral blood volume (CBV), cerebral blood flow (CBF), time to peak, and mean transit time were calculated. The topographic pattern was categorized into absence of asymmetry, watershed zones, and vascular territory hypoperfusion. A grading system of qualitative assessment of brain perfusion in region of interest was applied as the following: 0 = complete perfusion; 1 = hypoperfusion with preserved CBV (a lower CBF, delayed time to peak, increased mean transit time, decreased

flow, and normal or elevated CBV); and 2 = hypoperfusion without adequate blood volume (i.e., decreased CBV). Improvement of brain perfusion after the procedure was defined as at least 1 categorical number decrease in the region of interest by the grading system.

Statistical analysis. Continuous data were presented as median (interquartile ranges). Discrete data were given as counts and percentages. Chi-square test or Fisher exact test (if the group's number is 5 or less) was used to compare groups of categorical data. The Kruskal-Wallis equality-of-populations rank test was applied to compare groups of continuous unpaired data. Paired continuous data were compared by the Wilcoxon signed rank test. Linear regression models were used to assess the correlation between the change in brain perfusion and the changes in the results of 5 neuropsychological tests. A 2-sided p value of <0.05 was considered statistically significant. Stata/SE version 11.0 for Windows (StataCorp LP, College Station, Texas) was used for statistical analyses.

Results

Patients. Sixty-one patients (44 men; age 68.9 ± 10.2 years, ranging 47 to 86 years), including 22 chronic ICAO and 39 severe ICA stenoses, were included in the analysis. Twenty-five patients (41%) had prior ipsilateral ischemic events, with 14 having their last event within 6 months (NASCET symptomatic [North American Symptomatic Carotid Endarterectomy Trial]). Six patients (10%) had a history of neck radiotherapy for malignancy. Twenty-one patients (34%) had contralateral ICA stenosis >50%, with 12 of them undergoing CS according to the established indications before the index procedure. Ipsilateral cerebral perfusion insufficiency was found in all 22 ICAO and 20 of 39 severe ICA stenosis patients by baseline CTP. There was a significant difference in baseline cerebral perfusion scores between ICAO and severe ICA stenosis groups (median and interquartile range: 2 [1 to 2] vs. 0.5 [0 to 2], $p < 0.001$).

Procedure. Technical success was achieved in 14 of 22 ICAO (64%) and in all 39 severe ICA stenosis. The reason of failure in ICAO patients was the inability to pass a guidewire across the occlusion. One patient with left ICAO had a small nonfatal ipsilateral intracranial hemorrhage 5 hours after successful recanalization and stenting, possibly due to hyperperfusion. The neurological condition was stabilized with medical treatment only, and the patient was discharged 1 week later. One patient with left symptomatic ICA stenosis had an embolic stroke during CS. After neurosalvage with intra-arterial thrombolysis, the neurological condition improved significantly, and the patient was discharged 10 days later with mild motor aphasia. These 2 patients were excluded from further NCF evaluation.

Grouping for analysis. Patients were divided into 3 groups for analysis based on the pre-procedural CTP and interventional results: group 1 (n = 8) consisted of those with ipsilateral abnormal cerebral perfusion and a failed CS procedure; group 2 (n = 33) consisted of those with abnormal ipsilateral cerebral perfusion and successful CS; and group 3 (n = 18) consisted of those with symmetrical cerebral perfusion and successful CS. Table 1 summarizes the baseline demographics and clinical characteristics in the different groups. There were no significant differences among groups, except for the lower incidence of hyperlipidemia in group 3.

Table 1 Baseline Characteristics Among Groups

	Group 1 (n = 8)	Group 2 (n = 33)	Group 3 (n = 18)	p Value
Male	7 (88)	24 (73)	12 (67)	0.544
Age, yrs	60.5 (55–77.5)	71 (65–78)	69 (60–75)	0.457
Hypertension	7 (88)	25 (75)	14 (78)	0.772
Diabetes mellitus	2 (25)	8 (24)	7 (39)	0.515
Hyperlipidemia	6 (75)	25 (76)	7 (39)	0.025
Smoking	5 (63)	17 (52)	11 (61)	0.742
Coronary artery disease	5 (63)	21 (64)	14 (78)	0.553
Peripheral artery occlusive disease	1 (13)	5 (45)	8 (44)	0.057
Prior myocardial infarction	1 (13)	2 (6)	1 (6)	0.607
Chronic renal insufficiency	0 (0)	2 (6)	2 (11)	0.784
LVEF	67 (64–70)	67 (62.5–73.5)	65 (60–72)	0.550
Prior neck radiotherapy	1 (13)	5 (14)	0 (0)	0.201
Prior ipsilateral ischemic event	3 (38)	16 (48)	4 (22)	0.160
NASCET symptomatic at procedure	0 (0)	8 (24)	4 (22)	0.394
Target ICAO	8 (100)	13 (39)	0 (0)	<0.001
Left ICA lesion	5 (63)	16 (48)	8 (44)	0.765
Contralateral ICA stenosis >50%	2 (25)	13 (39)	6 (33)	0.802
Procedure success	0 (0)	33 (100)	19 (100)	

Values are n (%) or median (interquartile range).

ICA = internal carotid artery; ICAO = internal carotid artery occlusion; LVEF = left ventricle ejection fraction; NASCET = North American Symptomatic Carotid Endarterectomy Trial.

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Table 2 Baseline Neurological and Neurocognitive Function Among Groups

	Group 1 (n = 8)	Group 2 (n = 33)	Group 3 (n = 18)	p Value
NIHSS	0 (0–1)	0 (0–0)	0 (0–0)	0.580
Barthel Index	100 (97.5–100)	100 (100–100)	100 (100–100)	0.608
ADAS	4.5 (3–6.5)	6 (4–9)	5 (4–8)	0.321
MMSE	28 (27–29)	27 (25–28)	28 (25–29)	0.189
Color Trails Test Part 1, s	70.5 (52.5–127.5)	100 (78.5–136.5)	74.5 (55–109)	0.195
Color Trails Test Part 2, s	115.5 (105.5–192)	180 (143–215.5)	151 (102–189)	0.181
Verbal fluency	27.5 (24–37)	24 (20–30)	28 (25–32)	0.286

Values are median (interquartile ranges).
ADAS = Alzheimer Disease Assessment Scale; MMSE = Mini-Mental State Examination score; NIHSS = National Institutes of Health Stroke Scale.

The pre-procedural NIHSS, Barthel Index, and results of 5 neuropsychological tests were similar among the 3 groups without statistical difference (Table 2).

Neurocognitive changes. Table 3 shows the changes of the neurocognitive and neurological functions between baseline and 3-month follow-up in the 3 groups. Significant improvement in ADAS-Cog (pre-procedure: 6 [4 to 9] vs. post-procedure: 5 [3 to 7], p = 0.002), MMSE (pre-procedure: 27 [25 to 28] vs. post-procedure: 28 [25 to 29], p = 0.004), and Color Trails Test Part 1 (pre-procedure: 100 [78.5 to 136.5] s vs. post-procedure: 97 [60 to 128.5] s, p = 0.003) were observed in group 2. By comparison, there was no significant change in all test parameters at follow-up in groups 1 and 3. NIHSS and Barthel Index were stationary in 3 groups at 3-month follow-up compared with baseline. Excluding ICAO patients in group 2, significant improvement in ADAS (pre-procedure: 6 [4.5 to 10.5] vs. post-procedure: 5 [3.5 to 6.5], p = 0.024) and MMSE (pre-procedure: 26.5 [25.5 to 28] vs. post-procedure: 28 [25.5 to 29.5], p = 0.016), and a trend of improved Color Trails Test Part 1 (pre-procedure: 99 [77 to 124] vs. post-procedure: 97 [55 to 124], p = 0.058), were still observed in the patients with severe ICA stenosis (Table 4). Comparing the changes of neurocognitive tests from baseline after stenting in different groups, only Color Trails Test Part 1 was statistically different among groups (group 1 vs. group 2 vs. group 3: 1.5 [−14 to 11.5] vs. −12.5 [−36.5 to 0.5] vs. −0.5 [−11 to 27], p = 0.0159), and the changes of ADAS and MMSE were no longer different (ADAS, group 1 vs. group 2 vs. group 3: 0.5 [−1 to 1.5] vs. −2 [−3 to 0] vs. −1 [−2 to 0], p = 0.0887; MMSE, group 1 vs. group 2 vs. group 3: 0.5 [0 to 1.5] vs. 1 [0 to 2] vs. 0 [−1 to 1], p = 0.2751).

Correlation with perfusion. Ipsilateral brain perfusion improvement at 3 months was documented in 28 of 33 (85%) patients in group 2, but none in groups 1 and 3. Significant correlation between the change in perfusion and the change in MMSE (r = −0.33, p = 0.01) (Fig. 1A) was noted. A possible correlation between the change in perfusion and the change in Color Trails Test Part 1 results (r = 0.21, p = 0.12) (Fig. 1B) was also noted. The correlations between the change of perfusion and the changes of ADAS (r = 0.10), Color Trails Test Part 2 (r = 0.11), or verbal fluency (r = −0.05) were weak.

Discussion

A decline in cognitive function caused by cerebral hypoperfusion has been termed "vascular cognitive impairment" (21). The causative relationship between carotid artery disease and cognitive impairment was first proposed by Fisher in 1951, based on a necropsy case (22). He also postulated that enhancement of cerebral perfusion by reopening ICA stenosis may have a salutary effect on cognition. Although the large, international randomized extracranial-to-intracranial artery bypass trial, EC/IC Bypass Study (International Cooperative Study of Extracranial/Intracranial Arterial Anastomosis), failed to show the benefit of stroke prevention in patients with ICAO (23), several case series of bypass surgery still revealed significant improvement in cognition, which may result from improved CBF (24,25).

By contrast, the temporary flow arrest to the already ischemic hemisphere by cross-clamping during the CE procedure may offset the benefit of improved final cerebral perfusion (26,27). Results of CE on cognition have been controversial (6,7). However, several studies did demonstrate that in patients with depressed CBF, uncomplicated CE may improve cognitive function. Fearn et al. (28) found improvement in attention after CE, especially in patients with severely impaired baseline cerebrovascular reserve from carotid stenosis. Kishikawa et al. (29) also showed an improved mean score of the block design test after CE in patients with impaired cerebral perfusion, but not in those with preserved cerebral perfusion. These findings suggested that cognition may improve in patients with flow-limiting carotid stenosis, because the impaired baseline CBF is restored by carotid revascularization.

In the present study, we further demonstrated the beneficial effect of reperfusion on cognition. In patients with baseline perfusion failure, we can detect significant improvement on NCF after successful reperfusion. Comparing the different outcomes of groups 2 and 3, and the correlation between increased brain perfusion and improved cognitive function, we confirmed the role of cerebral hemodynamics in cognitive outcome in CS patients. The "learning effect" in patients re-evaluated after a short interval is a major concern, and may have confounded the interpretation of results in a number of prior studies showing cognitive improvement

Table 3 Differences of Neurocognitive and Neurological Function Between Baseline and 3-Month Follow-Up Among Groups

	Group 1 (n = 8)			Group 2 (n = 33)			Group 3 (n = 18)		
	Baseline	3 Months Post-Procedure	p Value	Baseline	3 Months Post-Procedure	p Value	Baseline	3 Months Post-Procedure	p Value
ADAS	4.5 (3–6.5)	5 (3.5–6)	0.669	6 (4–9)	5 (3–7)	0.002	5 (4–8)	6 (3～7)	0.301
MMSE	28 (27–29)	28.5 (26.5–30)	0.309	27 (25–28)	28 (25–29)	0.004	28 (25–29)	28 (25～29)	0.605
Color Trails Test Part 1, s	70.5 (52.5–127.5)	63.5 (55.5–136)	0.944	100 (78.5–136.5)	97 (60–128.5)	0.003	74.5 (55–109)	77 (51～120)	0.296
Color Trails Test Part 2, s	115.5 (105.5–192)	130 (96–206.5)	0.726	180 (143–215.5)	174.5 (138–218.5)	0.507	151 (102–189)	145.5 (105～197)	0.794
Verbal fluency	27.5 (24–37)	31.5 (27–37)	0.623	24 (20–30)	28 (21–32)	0.681	28 (25–32)	29 (25～35)	0.256
NIHSS	0 (0–1)	0 (0–1)	1.000	0 (0–0)	0 (0–0)	0.564	0 (0–0)	0 (0～0)	1.000
Barthel Index	100 (97.5–100)	100 (97.5–100)	1.000	100 (100–100)	100 (100–100)	0.564	100 (100–100)	100 (100～100)	0.317

Values are median (interquartile ranges).
Abbreviations as in Table 2.

Table 4 Neurocognitive and Neurologic Function at Baseline and 3 Months Post-Procedure in the Patients With Severe ICA Stenosis and Objective Baseline Abnormal Cerebral Perfusion (n = 20)

	Baseline	3 Months Post-Procedure	p Value
ADAS	6 (4.5–10.5)	5 (3.5–6.5)	0.024
MMSE	26.5 (25.5–28)	28 (25.5–29.5)	0.016
Color Trails Test Part 1, s	99 (77–124)	97 (55–124)	0.058
Color Trails Test Part 2, s	160 (129–199)	171 (124–207)	0.657
Verbal fluency	25 (23–29.5)	27.5 (21.5–31.5)	0.910
NIHSS	0 (0–0)	0 (0–0)	1.000
Barthel Index	100 (100–100)	100 (100–100)	0.971

Values are median (interquartile range).
ICA = internal carotid artery; other abbreviations as in Table 2.

after carotid revascularization (6,7). The design of the present study, however, mitigated this limitation completely. Group 1 served as a perfect control, which not only had similar baseline characteristics and perfusion status to group 2, but also underwent a "sham" procedure. The results therefore excluded the learning effect of tests done at short intervals.

CS is associated with shorter ipsilateral carotid flow interruption compared with CE (26), but it may carry a higher risk of microembolization (26,30,31). Subclinical microembolization during cardiac catheterization or surgery is known to affect cognitive performance, despite the silent neurological manifestation (32,33). Transient hypotension occurs frequently in patients undergoing CS (34), and may also worsen cerebral perfusion in patients with tandem or diffuse intracranial arterial diseases. The net benefit of improved CBF on cognitive outcome after CS may thus be offset and neutralized. Hence, it is understandable that results of cognitive outcome after CS may be inconsistent (7). We believe the design and results of the present study demonstrate the benefit on cognition of restoring perfusion by CS. In fact, this beneficial effect may be more potent than our finding, because microembolization and systemic hypotension are inherent to the procedure.

Different neurocognitive tests are designed to evaluate different aspects of NCF. Although ADAS-Cog and MMSE are nowadays the most commonly applied tools to assess global cognitive function, they can only assess relatively stable aspects of cognition and stratify the severity of cognitive impairment in the population of mild-to-moderate dementia. There might be a "ceiling effect" in patients with minimal cognitive impairment, who constitute the majority of the population with carotid stenosis. According to a previous review of neurocognitive effects of CE (35), domains containing psychomotor speed/reaction time, attention, memory, and visuoconstructional organization (such as Color Trails Test Part 1) may be more consistent and sensitive in showing improvement after carotid revascularization. That is probably why significant changes from baseline could be observed only in the Color Trails Test Part 1 in this cohort.

Study limitations. Despite the overall cognitive improvement in group 2, there are still individual variations in the

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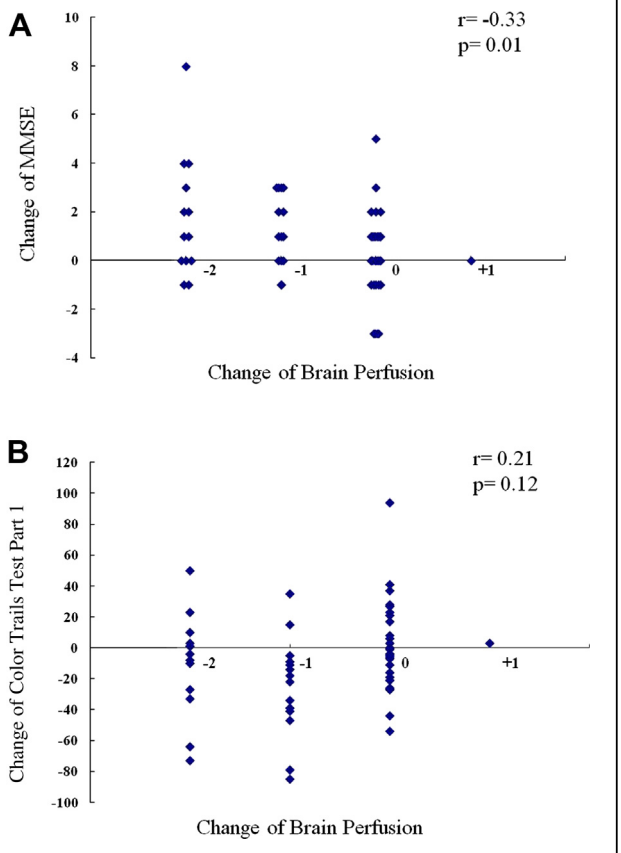

Figure 1 Correlation of Brain Perfusion Changes to NCF Tests

(A) The correlation between the change in brain perfusion and the change in Mini-Mental State Examination (MMSE) after the procedure. **(B)** The correlation between the change in brain perfusion and the change of Color Trails Test Part 1. The correlation coefficient (r) and p value are shown. NCF = neurocognitive function.

magnitude of changes in patients and tests. A larger number of patients and more functional-specific or topographical neuropsychological tests and imaging modalities will be mandatory in the future. For example, magnetic resonance imaging before and after a procedure may help to better quantify prior infarct area and procedure-related microembolism. Metabolic imaging such as 18F-fluorodeoxyglucose positron emission scanning may help to correlate anatomic reperfusion and recovery of specific cortical functions after CS. The follow-up interval in the present study was relatively short, and a longer observation period is needed to demonstrate long-term improvement in cognitive function. One intracranial hemorrhage and 1 embolic stroke occurred in this small series, and the cognitive benefits need to be balanced by procedural risk in the future larger population, especially in asymptomatic patients.

Conclusions

We concluded that successful CS can improve NCF in patients with severe ICAO and objective abnormal cerebral perfusion. The improvement of cognition correlated well with the improvement of ipsilateral brain perfusion.

Reprint requests and correspondence: Dr. Hsien-Li Kao, Department of Internal Medicine, National Taiwan University Hospital, 7 Chung-Shan South Road, 100 Taipei, Taiwan. E-mail: hsienli_kao@yahoo.com.

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